II

THE PROPHYLAXIS OF NEURO-SYPHILIS

Discussion

Dr. Paul Fildes explained that for some years he had been rather out of this line of work, but he still had some interest in the prevention of the disease, and he would like to take the opportunity of putting some questions, particularly to the President.

The prevention of syphilis of the nervous system obviously depended on the efficiency with which the original infection was dealt with. And the liability to neuro-syphilis might be diminished by increasing the efficiency of anti-syphilis drugs. Neuro-syphilis would decrease in proportion as the public were educated as to the importance of early diagnosis and treatment. Any one who adopted local treatment for a supposed syphilitic lesion was increasing the incidence of neuro-syphilis. A large proportion of cases of syphilis had, in early stages, meningitis of varying degree, but seldom accompanied by clinical signs of lesions of the central nervous system. He believed that the present situation in regard to early meningitis cases and their subsequent fate was not further advanced than in 1912. It was remarkable that though ten years ago hundreds of men in the Navy had lumbar puncture done on them for early syphilis, there was no information available as to their subsequent fate. He would like to know if the President would be able to give this information or have it collected. It would enable the profession to know whether early meningitis had any bearing on subsequent parasyphilitic disease. It was difficult to get such facts from civil practice. Persons with the more marked meningitis in the early stage would be more likely to be cured than others who had it slightly, and so were less likely to become parasyphilitics. The degree of meningitis constituted some index of the permeability of the cerebral vessels. The difficulty was

that salvarsan and its like would not cross the cerebral capillaries. Anti-toxins did not get into the brain either. It seemed to him possible that in the cases which showed severe reactions after salvarsan treatment, cure was more likely, *qua* nervous syphilis, than the cases having a less severe reaction.

The question of increasing the efficiency of anti-syphilitic drugs was a highly theoretical one, and was bound up with that of the permeability of cerebral vessels. These drugs could only affect the meningeal spirochætes, not those in the parenchymatous tissue of the brain. This permeability therefore offered a tempting field for study. Some French authorities believed it was possible to obtain a passage of anti-bodies in serum through the cerebral capillaries into the brain by the intravenous injection of urotropin at the same time as the injection of anti-toxin ; he did not know whether that had been tried in connection with syphilis. McIntosh and he had worked on the matter, and tried to get comparable results by working on aniline dyes. They found there was a remarkable obstruction to the penetration of a substance like fluorescine into the brain. The only substances with which they succeeded in this way were neutral red and methylene blue, and they concluded it was a question of the solubility of these dyes ; these last two named were soluble in chloroform, while the others were not. They then tried to produce an arsenical compound which was soluble in chloroform (with the assistance of a chemist), and the chemist did produce a combination of neutral red and arsenic which was soluble in chloroform and penetrated into the brain. The difficulty was that the animals experimented on subsequently died. These arsenical compounds were very toxic, and some of the severe brain reactions in cerebral syphilis after salvarsan treatment might be due to some of the drug having got into the brain in consequence of the inflammation. Still, the matter was well worthy of study.

Dr. DAVID LEES complimented the opener on the excellence of his paper. In his opinion the whole subject of the prophylaxis of neuro-syphilis was dependent on the efficient treatment of early syphilis. Lack of treatment and inefficient treatment of syphilis in its earlier stages was responsible more than anything else for neuro-syphilis, and a great deal of work still required to be done

to educate the profession as to the minimum amount of treatment which is essential in every case of syphilis. He deprecated the talk about aborting syphilis, because it tended to make medical men under-treat the disease. In every case of syphilis the central nervous system should be examined clinically, and it was advisable to repeat this examination at the end of each course of treatment. In every case also the cerebrospinal fluid should be examined immediately, if there was any suspicion of clinical involvement of the central nervous system, and even if no clinical signs were apparent, it should always be examined at the end of the first year of treatment. It did not follow that every case which showed pathological changes in the fluid in early syphilis suffered at a later date from neuro-syphilis. It was very probable, however, that such cases, if untreated or partially treated, would do so, and such cases should invariably have more intensive treatment and be watched for longer periods than cases which showed a normal cerebrospinal fluid. He was under the impression that medical men were in some cases apt to regard somewhat lightly the dangers of syphilis and especially of neuro-syphilis. Many were content with the disappearance of the signs and symptoms of syphilis, many more failed to think of examining the cerebro-spinal fluid. Even if a patient suffering from syphilis showed cerebral symptoms or signs of disease, the physician in charge was apt to be quite content when the patient recovered from the brain storm, and many of those patients after apparent recovery received no further observation and practically no specific treatment. Any patient with specific involvement of the central nervous system must be under observation from time to time, and in every case the cerebrospinal fluid should be examined and proved normal before the patient could be considered as anything akin to cured. Clinical improvement was certainly desirable, and clinical cure was essential in every case. Unless, however, the cerebro-spinal fluid was free from pathological involvement, the permanence of the cure was unlikely.

As to pregnancy—he agreed that syphilis in the mother was more important than in the father as far as heredity was concerned, and he hesitated to allow any infected person to marry before they had undergone careful and continuous treatment for at least two years. In any case

in which the blood had not reacted to treatment, he advised intensive treatment for two years, but more moderate treatment subsequently, and he was of opinion that a period of at least five years should intervene before such person should marry. In every such case he was of opinion that the partner of the marriage should be cognisant of the risks which were involved. The pregnant woman who suffered from syphilis reacted extremely well to treatment, and the results of this prophylactic treatment during pregnancy were so efficient that every mother suffering from syphilis should be given the advantage of it.

The prevention of neuro-syphilis and of syphilis was dependent on the education of the medical profession and of the public. Every undergraduate in medicine must be impressed with the fact that the disappearance of the signs of syphilis did not necessarily mean cure, and that treatment must be continued for a very considerable time afterwards. The period of observation in any case must not be considered, even yet, as less than two years.

Colonel L. W. HARRISON said, with regard to the nature of the treatment in the early stages of syphilis, he had come tentatively to the conclusion that, if one treated syphilis in the early stages with arsenobenzol only, there was much more likelihood of neuro-recurrence than if mercury or bismuth were given simultaneously with it. In the early days of " 606 " there was a large incidence of neuro-syphilis, and in his own experience, practically all the cases which had relapsed with clinical signs of neuro-recurrence had received " 606 " only.

A paper by Moore and Kemp, in the *Johns Hopkins Hospital Bulletin* for July last year, seemed to support the view he had just expressed. At that clinic the method was to give a course of the original " 606," then a course of mercury, then " 606 " again, and so on for a number of months. But in 2,500 early cases of syphilis there had been 56 cases of clinically manifest neuro-syphilis there. In approximately the same number of early cases treated in his, the speaker's, own clinic, on the simultaneous arsenobenzol with Hg or Bi plan, there had not subsequently been a single case of clinically manifest neuro-syphilis.

Dr. Fildes seemed to indicate that the more severe the early meningeal trouble, the less likely were such develop-

ments as tabes and G.P.I., and that seemed to accord with Colonel Harrison's experience. He wondered how many cases of tabes and G.P.I. neurologists had seen in whose history there had been anything in the nature of early clinical neuro-syphilis. Generally, neurologists he had asked on this point had said they had seen no such cases, and the speaker suggested that a severe meningeal reaction might create some immunity in the neighbouring tissues. Around a syphilitic lesion on the skin there seemed to be a zone of immune tissue, and it might be that the same occurred in the central nervous system.

It was probably difficult for Naval authorities to get the information in regard to the present state of men who were in the Navy ten years ago, as so many of them must now be in civil life, but an attempt had been made to investigate the later histories of soldiers who were treated for syphilis during the War, from the point of view of neuro-syphilis ; this Society had issued a questionnaire to all clinics on this point, and the results published in the BRITISH JOURNAL OF VENEREAL DISEASES had shown that a very meagre number of such cases had been discovered, though approximately 100,000 British soldiers were treated for the disease during the War.

As to the relation of injury or overwork to tabes and G.P.I., he believed strongly there was a close relation between overwork or injury and recurrence of syphilis in any part of the body.

Dr. WILFRID S. FOX said he felt much indebted to Dr. Ironside for his opening paper, and he was specially interested in the figures given by him showing a drop in the incidence of neuro-syphilis under modern treatment. He had felt that there was a drop, but not so great as Dr. Ironside's figures showed. He thought that the results of cases, whether treated in the primary pre-Wassermann stage, or when that reaction had become positive, and the secondary rash was well out, must be accepted with considerable caution.

It was perhaps contrary to the usual teaching, but the speaker's experience was that just as good results were obtained by beginning treatment in the early secondary stage, when the Wassermann was strongly positive, as in the early primary stage before the Wassermann reaction came into action.

With regard to marriage, the whole subject bristled

with difficulties. It was as well to have a rule, but in practice each case had to be treated on its merits, and one of the most important points was the mentality of the patient.

Many speakers advocated the examination of cerebrospinal fluid at stated intervals, and although he thought it was a very sound guide to the doctor, it was sometimes difficult to get the patient to submit to it a second time if he had severe headache and vertigo on the first occasion.

Another point was that one read in literature that if a patient's blood remained negative for eight months it would keep permanently so, but in two cases of his own there had been a negative finding for two years, then three months without treatment brought them back with a slightly positive Wassermann.

Dr. HANSCHELL. In certain human and animal trypanosome infections there occurred an actual invasion of the brain parenchyma by the trypanosomes ; these could be demonstrated in the cerebrospinal fluid by thecal puncture. Intrathecal therapy had failed. But lately Mr. Edwards, in India, had shown this was perhaps because too large doses had been given. Calculating dose according to weight of brain and spinal cord, and not according to total body weight, Edwards had given arsenic intrathecally and cured ponies suffering from *surra*, in the ponies' C.S.F. *Trypanosoma Evansi* had been demonstrated before treatment. Dr. Hanschell had tried treatment on those lines in one case of advanced human G.P.I. (a big man) and found that up to 6 mgm. of novarsenobenzol, dissolved in sterile distilled water, was apparently well tolerated by that patient when injected intrathecally in the lumbar region. Ultimately there had been no improvement. On the contrary, some weeks after the last intrathecal injection this patient rapidly got worse ; he was now moribund.

Dr. DAVID NABARRO said he had injected novarsenobenzol into the central nervous system without ill effect. He had treated three cases of G.P.I. by intrathecal injection of salvarsanised serum *via* the cisterna magna. In the first case, after the injection the fluid was much better, and later became negative. A case in a child was that in which there suddenly developed mania. Six injections of the serum were made into her cisterna magna, and this was followed by a course of malaria, this suc-

ceeded again by more serum. She was now, to all intents and purposes, a healthy child, though there had probably been some destruction of brain tissue.

In Uganda in 1903 he had himself tried intravenous injections of methylene blue in a case of sleeping sickness, and it intensely fixed itself in the central nervous system.

Two cases had been sent to him by a colleague on account of "indigestion," which was thought by that doctor to be in the nature of crises in tabes. The blood of both was strongly Wassermann positive. In neither was there a history of a primary lesion, though both confessed to gonorrhœa. The latter, if occurring at the same time as syphilis, might possibly mask the primary and even the secondary lesions of the latter.

Neuro-syphilis in children had interested him very much, and he had examined the spinal fluid of 300 such children. His experience was that the spinal fluid was not often positive in congenital syphilis. He was now trying what effect malaria treatment by itself might have. Prolonged treatment by intravenous injection had no effect on the spinal fluid in some cases.

Mr. C. MILLS was surprised to hear some members reverting to intrathecal injections of salvarsanised sera, as most people had concluded now that it was wrong therapy.

Speaking on the general question, he said the point at which to aim was educating first the profession, then the public, as to the importance of cases of syphilis coming for treatment at the earliest possible date, for then the spirochæte was accessible.

Mr. WANSEY BAYLY said he could not understand why Dr. Lees objected to syphilitic women marrying until after three, four, or five years of treatment, seeing that he had admitted that a woman treated during her pregnancy usually bore a healthy child. If a syphilitic had had a year of efficient treatment and agreed to continue the treatment after marriage, that should suffice. That was his method, and he was not aware of any unfortunate results. He agreed the man should inform his prospective bride of the danger, but if all risks of possible but remote danger or death was going to prevent marriage, few marriages would take place. It was a question of the proportion of risk. Mr. Bayly said that his experience suggested that there was less likelihood of recurrences

if patients began treatment at the beginning of the secondary stage than if treatment was started during the primary stage, perhaps because at the secondary stage immune bodies had developed to a considerable extent. It was impossible to say what was efficient treatment. Just before the War he had two cases of syphilis in the early secondary stage, to each of which two injections only of salvarsan were given. He saw both after the War, and one had developed neuro-syphilis, while the other had married and produced a healthy family, and showed neither pathological nor clinical evidence of infection.

A point which had not been touched on in this discussion was the prevention not only of neuro-syphilis, but of all syphilis. He referred to the education of the public on the preventive value of immediate self-disinfection after risk.

Dr. DOROTHY LOGAN said a colleague had a girl who came to hospital for treatment for secondary syphilis; she was early in pregnancy and had not aborted. She was thoroughly treated, and at full term was healthy. The first stage of the labour was long, and there was some obstetric disaster, causing the baby's death. It appeared to be a fine, large, healthy babe, but its liver and spleen were found, *post mortem*, to be full of spirochætes. It caused the speaker to think a lot about supposedly healthy babies born after the syphilitic mother had been treated during her pregnancy.* She also mentioned the case of a young woman who, in consequence of infection, was strongly advised not to marry. She acted on this, but became pregnant instead!

Dr. SHARPE said he thought there was some danger in awaiting the secondary stage before commencing treatment, as some of the cases which developed nervous lesions afterwards had not had an obvious secondary stage at all.

The PRESIDENT thanked Dr. Ironside for having introduced a discussion which had been very popular, and the matter would be continued on May 27th, when Dr. George Riddoch would make a contribution.

DR. IRONSIDE, in reply, said Dr. Fildes' work clearly showed that the cerebro-spinal fluid was abnormal. The non-appearance of cutaneous eruptions in cases of late neurosyphilis was of great interest; neurologists had

* Apropos of telling patients that they are not in a fit state to marry.

noticed it for many years. With regard to the frequency of manifest syphilis of the nervous system, the figure he gave referred to meningeal reactions of all types.

He asked, Could the methods of treating primary syphilis be improved, either by a combination of drugs, as Colonel Harrison suggested, or by discovering a drug which could penetrate the meningeal vessels? It was known what happened to the people who were treated, and often syphilologists did not see the outcome of their cases. Of course lumbar punctures were disagreeable, but they were important; the fluid might furnish the only sign that the nervous system was involved in the disease. Most specific patients tolerated the puncture well.